REMARKS

The claims have been amended to clarify the invention. In particular, claim 1 has been amended to recite a naturally occurring variant of SEQ ID NO:1 having at least 95% sequence identity to SEQ ID NO:1. Support for this amendment is found in the specification, for example, at p. 9, lines 13-19, and at p. 11, lines 5-8. Claim 2 has been amended to delete the recitation of non-elected inventions. No new matter is added by these amendments, and entry of the amendments is therefore requested.

35 U.S.C. § 101, Rejection of Claims 1-6

The Examiner has rejected claims 1-6 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific asserted utility or a well established utility. The Examiner summarized claims 1-6 and stated that the disclosed utilities for the polynucleotide of SEQ ID NO:2 or MRTM (SEQ ID NO:1) include diagnosis and treatment of cancer, in particular breast cancer, production and screening of antibodies that specifically bind SEQ ID NO:2 (sic, SEQ ID NO:1). The Examiner stated that neither the specification nor any art of record teaches what SEQ ID NO:2 is, what it does do, do not teach a utility for any of the fragments or the derivatives claimed, and do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

The Examiner stated that the asserted utilities apply to many unrelated polypeptide structures sequences and therefore are not considered specific utilities, i.e., they are not specific to SEQ ID NO:2. The Examiner stated that the asserted utility for SEQ ID NO:2 is based on the assertion that SEQ ID NO:1, encoded by SEQ ID NO:2, has chemical and structural homology to mucin proteins, and in particular, SEQ ID NO:1 and human mucin MUC3 and porcine gastric mucine PGM-9B share 26% identity. The Examiner then summarized various structural and possible functional sequence motifs recited in SEQ ID NO:1 at pp. 10-11 of the specification, including the EGF-like domains and a predicted transmembrane domain, and further acknowledged that SEQ ID NO:2 is over expressed in a breast tumor cancer cell line, BT20, as compared to normal mammary epithelial cells. The Examiner further acknowledged applicants disclosure that various human mammary epithelial tumor cell lines at various stages of breast cancer are a useful model to study the process of malignant transformation and tumor progression in breast cancer (see Wistuba et al. (1998), IDS reference # 12).

The Examiner stated, however, that the specification does not disclose any actual biological activity of SEQ ID NO:1, nor any data confirming that the portion from C594 to C627 of SEQ ID NO:1 has any biological activity. The Examiner then summarized the teachings of a number of articles alleged to

support the Examiner's contention that the effects of dissimilarities between SEQ ID NO:1 and the mucin proteins upon protein structure and function cannot be predicted. See Bowie et al (1990); Burgess et al. (1990): Lazar et al. (1988); Bork (2000); and Scott et al.(1999). The Examiner concluded that, given these teachings, with a 74% dissimilarity between SEQ ID NO:1 and the mucin proteins, the function of SEQ ID NO:1 could not be predicted.

The Examiner further stated that although the specification discloses overexpression of SEQ ID NO:2 in breast cancer cell line BT20 as compared to normal cells, the cell lines studied by Wistuba et al. are specific cell lines that are cultured form a subset of primary breast carcinomas whereas it seems that the BT20 cell line studied in the claimed invention is not the same as the cell lines studied by Wistuba et al. Thus it is unpredictable that the BT20 cell line has any of the properties of the cell lines studied by Wistuba et al. The Examiner then stated that it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. The Examiner cited and discussed several literature references alleged to support this conclusion. See Drexler et al. (1993); Embleton et al. (1984); Hsu (1973); Mustafa et al. (1996); Freshney (1983); and Demer (1994). The Examiner concluded by stating that "Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions".

Applicants Response

Applicants disagree that the specification supports neither a specific and substantial asserted utility or a well established utility for the claimed invention. The Examiner is first of all reminded of the legal standard for utility as applied to patentable inventions. To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

Applicants would first like to address the Examiner's allegation that it is well known in the art that cell lines are generally recognized as an unsuitable model for the study of any kind of human cancer, either for diagnostic or therapeutic purposes. It is first of all noted that none of the articles cited by the Examiner specifically address the use of breast cancer cell lines in the study of breast cancer detection and diagnosis, in particular, the BT20 cell line. Further, none of the cited articles make such a sweeping conclusion regarding the irrelevance of using cell lines in general for screening for potential cancer diagnostics. Most of these articles merely address the issue that cells in culture may differ significantly from their in vivo counterpart with regard to their growth in monolayer culture versus three-dimensional geometry (e.g., Freshney) and may differ antigenically from in vivo tumors (e.g., Embleton). These articles mostly address the fact that cell culture models, alone, do not reliably predict the effects of potential therapeutic agents on in vivo tumors. None of these articles specifically address the issue as to whether or not cell lines, such as BT20, are suitable for identifying genes specifically expressed, or differentially expressed, in various human cancers. Thus the Examiner's sweeping conclusion that these articles somehow support an allegation that cancer cell lines are generally unacceptable models for the identification of prognostic or diagnostic indicators of cancer, in particular, breast cancer is unfounded.

In contrast, various articles cited in the instant application support the use of cancer cell lines, in particular breast cancer cells, for just this purpose. For example, the Wistuba article (IDS reference # 12) attests to the generally acceptable use of breast cancer cell lines derived from primary breast carcinomas as suitable model systems for biomedical studies, and the Examiner does not refute this. The Examiner merely notes that the BT20 cell line is not specifically recited in the article. While the Wistuba article does not specifically recite the BT20 cell line, it clearly makes the point that the principle problem with using cell lines for screening studies is the ability to successfully culture them for long periods of time, and therefore that those that can be serially cultured are reliable models for breast cancer. In addition, many of the other articles cited in the application support the use of breast cancer cell lines, including the BT20 cell line, in modeling human breast cancer. The Zhou article (reference # 7) describes the use of the human breast cancer cell line, HBL-100 in studying the down-regulation of the human secreted frizzled-related protein, hsFRP, in human breast cancers; The Sager article (reference # 10) describes identifying the expression of the tumor suppressor, maspin, in normal but not tumor derived mammary epithelial cells, and the effects of this differential expression on both mammary and prostate tumor cells in culture; the Lee article (reference # 11) describes the down-regulation of a member of the S100 gene family in mammary carcinoma cell in culture, including the BT20 cell line; and the Williams

article (reference # 13) describes the use of colon tumor cell lines specifically to identify the expression of mucin genes, the subject of the instant application, in colon cancers. In addition, Applicants have attached abstracts of three more recent articles as evidence that breast cancer cell lines, in particular the BT20 mammary carcinoma cell line, continue to be used as models for studying the expression of genes associated with human breast cancer. See Mitchell et al. (2002) Neoplasia 4:9-18, Exhibit A; Williamson et al. (2002) Breast Cancer Res Treat 74:155-165, Exhibit B; and Chen et al. (2000) Biochem Biophys Res Commun 277:757-763, Exhibit C.

Thus the Examiner's evidence supporting her allegation that the BT20 breast cancer cell line is not an acceptable model for predicting diagnostic indicators for breast cancer clearly does not meet the standard of proof provided by law that a preponderance of evidence supports her position, and in fact ignores many other articles supporting this use. Neither does the Examiner's evidence support the allegation that one skilled in the art would doubt a "substantial likelihood" that the claimed polynucleotide would be a useful diagnostic marker for breast cancer.

For all of the above reasons, applicants submit that a specific and substantial asserted utility for the claimed invention in the detection and diagnosis of breast cancer is fully supported by the specification, and therefore request withdrawal of the rejection of claims 1-6 under 35 U.S.C. § 101.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1-6

The Examiner has rejected claims 1-6 under 35 U.S.C. § 112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner noted that a complement, as recited in claims 1 and 2, could be partial or complete, wherein a partial complement could share with SEQ ID NO:2 only a few common nucleotides. The Examiner stated further that the claims read on polynucleotide variants of SEQ ID NO:2 wherein said variants have any type of substitution besides conservative substitution, at any amino acid throughout the length of the nucleic acid or peptide as well as insertions or deletions provided that the resulted variation is up to 10% difference with SEQ ID NO:2. Structural features, that could distinguish the claimed structural polynucleotide variants and nucleotide sequences encoding polypeptide variants from the nucleotide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed. In addition, the Examiner stated, no common functional attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the

polypeptide variants are disclosed, because the function of a nucleotide sequence is abolished even with substitution of only one amino acid (Burgess et al., 1990). Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. The Examiner quoted *Vas-Cath v. Mahhurkar* with respect to the principle that the invention, for the purposes of the written description inquiry, is *whatever is now claimed.* The Examiner also cited The *Regents of the University of California v. Eli Lilly* with respect to the courts holding that a generic statement which defines a genus of nucleic by *only* their functional activity does not provide adequate written description of the genus, and further cited *Fiers v Revel* with respect to the holding that adequate written description requires more than a mere statement that it is a part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required.

Applicants Response

Claim 1 has been amended to recite SEQ ID NO:1, and a naturally occurring variant of SEQ ID NO:1 having at least 95% sequence identity to SEQ ID NO:1. Claim 2 recites a "naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity to SEQ ID NO:2".

Applicants first of all note that the definition of the "complement" of a cDNA of the invention is recited at p. 6, lines 26-28 of the specification as a cDNA "---which is completely complementary over its full length---", and therefore that the use of the term, as recited in the claims, explicitly excludes "partial" complementarity.

With respect to variants of the polypeptide sequence of SEQ ID NO:1 and SEQ ID NO:2, Applicants submit that the requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law, some of which the Examiner has recited in support of her rejection under this statute:

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical

> and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the application (see, for example, page 3, lines 20-22. Variants of SEQ ID NOs:1 and 2 are described, for example, at page 3, lines 23-24, and at p. 4, lines 18-19. Incyte clones in which the nucleic acids encoding the human MTRM were first identified and libraries from which those clones were isolated are described, for example, at page 9, lines 28-33 of the Specification. Chemical and structural features of MTRM are described, for example, on page 10 through p. 11, line 32. Given SEQ ID NOs:1 and 2, and the described chemical and structural features of SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having 95% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because

> ---the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus.
>
> (page 17 of the Office Action)

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

1. An isolated cDNA or the complement thereof comprising a nucleic acid sequence encoding:...b) a naturally occurring variant of SEQ ID NO:1 having at least 95% identity to the amino acid sequence of SEQ ID NO:1...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In particular, the extensive chemical and structural features characterizing SEQ ID NO:1 and related mucin proteins given at pp. 10-11 of the specification clearly encompass common structural attributes that identify the claimed polynucleotide variants, in opposition to the Examiner's contention. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Exhibit D). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to mucin-related proteins related to the amino acid sequence of SEQ ID NO:1 (MRTM). In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as MRTM proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1 The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 946 amino acid residues). This variation is far less than that of all potential mucin proteins related to SEQ ID NO:1, i.e., those mucin proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a filing date of April 2001. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application. Withdrawal of the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph for lack of written description is therefore requested.

35 U.S.C. § 112, First Paragraph, Enablement Rejection of Claims 1-6

The Examiner has rejected claims 1-6 under 35 U.S.C. § 112, first paragraph, specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in

the rejection under 35 U.S.C. § 101 above, one skilled in the art clearly would not know how to use the claimed invention.

For the reasons set forth above in response to the rejection of these claims under 35 U.S.C. § 101, the claimed invention is supported by a specific and substantial asserted utility and therefore that one skilled in the art would know how to use the claimed invention. Withdrawal of the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, is therefore requested.

35 U.S.C. § 112, First Paragraph, Scope, Rejection of Claims 1, and 4-6

1. The Examiner further stated that, if Applicant could overcome the above 101 and 112, first paragraph rejection, claims 1 and 4-6 are still rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a polynucleotide of SEQ ID NO:2, does not reasonably provide enablement for a polynucleotide "encoding" SEQ ID NO:1. The specification discloses isolation of SEQ ID NO:2 which is overexpressed in a breast cancer cell line. However, the Examiner stated, there is no evidence that the deduced SEQ ID NO:1 is expressed in any tissue. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. The Examiner then cited various art allegedly supporting her contention that the predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. See, in particular, Shantz and Pegg (1999); McClean and Hill (1993); Fu et al. (1996); and Yokota et al. (1988), Office Action, pp. 19-20.

Applicants Response

With respect to the issue of whether the polypeptide encoded by the claimed polynucleotide is expressed in nature and/or at a level sufficient for its intended use, the Office Action has set forth the novel theory that the central dogma of molecular biology (*i.e.*, DNA directs transcription of messenger RNA which in turn directs translation of protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:2 (which encodes the polypeptide of SEQ ID NO:1) was determined from a human cDNA library. That cDNA library in turn was made from messenger RNA isolated from human tissue. See the Specification, for example, at pages 25 to 26. Thus, the nucleotide sequences of the present invention are expressed sequences. The Office Action purports that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter lacks patentable utility.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. While steady state mRNA levels are not

always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites several examples of protein regulation downstream of transcription; however, these examples represent comparatively unusual mechanisms of gene regulation. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages attached as Exhibit E):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation o transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:2 mRNA. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels.

Applicants therefore submit that for the above reasons, a polynucleotide encoding SEQ ID NO:1 is enabled by virtue of the differential expression of the encoding polynucleotide, SEQ ID NO:2, in breast cancer, therefore providing a substantial likelihood that the protein of SEQ ID NO:1 is similarly differentially expressed.

2. The Examiner stated that if applicant could overcome the above 101 and 112, first paragraph rejection, claim 2 is still rejected under 35 U.S.C. § 112, first paragraph, because the

specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for variants of SEQ ID NO:2. Applicants have not shown how to make or use the claimed variant polynucleotides, and nucleotide sequences encoding the polypeptide variants which are capable of functioning as that which is being disclosed. The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology, and that such unpredictability would equally apply to DNA sequences which encode proteins. The Examiner then cited various references alleging to support her contention that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. See Burgess et al. (1990); Lazar et al. (1988); and Tao et al. (1990). The Examiner further stated that, in addition, although conservative substitution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) are naturally subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Applicants Response

Applicants first of all submit that, as stated in the response to the rejection of these claims under 35 U.S.C. § 112, first paragraph regarding possession of the claimed variants, variants of SEQ ID NO:1 and SEQ ID NO:2 are described in chemical and structural terms rather than functional terms and there is therefore no requirement for the claimed variants to be capable of "functioning as that which is disclosed". One skilled in that art would be able to identify the claimed variants from naturally occurring mucin-related proteins or polynucleotides based on the disclosures discussed previously, and to "make" said variants by methods routine in the art.

The uses of the polynucleotides of the invention, including variants of SEQ ID NOs:1 and 2, are described and enabled throughout the specification, e.g., as hybridization probes (see page 13); for the diagnosis of disease conditions (see page 17); for chromosomal mapping (see page 14, lines 12-16 and page 31, lines 20-28); and in microarray assays to monitor gene expression patterns (see page 14, lines 4-11 and page 36, Example X). None of the described uses of the polynucleotides require a functional association of an encoded polypeptide. In particular, the use the various polynucleotides of the invention "in hybridization, amplification, and screening technologies to identify and distinguish among SEQ ID NO:2 and related molecules in a sample" (p.11, lines 24-25) does not depend on whether or not such variants might be non-functional.

Thus variants of the SEQ ID NO:2 and polynucleotides encoding SEQ ID NO:1 are fully enabled by the specification for this purpose.

3. The Examiner stated that if Applicant could overcome the above 101 and 112, first paragraph rejection, claims 1-6 are still rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for the "complement" of SEQ ID NO:2, or a nucleic acid sequence encoding SEQ ID NO:1 or a naturally occurring variant thereof. It is noted, the Examiner stated, that a complement could be partial or complete complement, wherein the partial complement could share with SEQ ID NO:2 only a few common nucleotides. The Examiner stated, therefore, that the claims encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to SEQ ID NO:2, that is polynucleotides that are complements to SEQ ID NO:2 or a nucleic acid sequence encoding SEQ ID NO:1 or a naturally occurring variant thereof, and that when given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. It would be expected that a substantial number of hybridizing molecules encompassed by the claims would not share either structural or functional properties with SEQ ID NO:2.

Applicants Response

As previously discussed in this response, the definition of the "complement" of a cDNA at p. 6, lines 26-28 of the specification recites a cDNA "---which is completely complementary over its full length---", and therefore that the use of the term, as recited in the claims, explicitly excludes "partial complementarity. The claims therefore do not encompass sequences "attached to SEQ ID NO:2 or a nucleic acid encoding SEQ ID NO:1 or a naturally occurring variant thereof" that are anything less than the full complement of these sequences and which would therefore share only identical structural or functional properties of these nucleic acid sequences.

For all of the above reasons, applicants submit that claims 1-6 are fully enabled by the specification, and therefore request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102(b), Rejection of Claims 1-2

The Examiner has rejected claims 1-2 as being anticipated by Nagase et al., Genbank Sequence Database (Accession AB033063), NCBI, National Library of Medicine, Bethesda,

Maryland (1999), or PN=5,849,578. Claims 1-2 are drawn to a "complement" of the nucleic acid sequence of SEQ ID NO:2 or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, and a naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity to SEQ ID NO:2 or the "complement" thereof.

Nagase et al. teach a polynucleotide which is 100% similar to SEQ ID NO:2 from nucleotide number 1533 to 6674. PN=5,849,578 teaches a polynucleotide (SEQ ID NO:7) which is 94% similar to SEQ ID NO:2 from nucleotide number 1 to 5441. Given the polynucleotide sequence taught by Nagase et al. or PN=5,849,578, the Examiner stated, one of ordinary skill in the art would immediately envision the claimed polypeptide.

Applicants Response

The amendments to claims 1 and 2 have ben discussed supra. Neither Nagase et al. nor PN=5,849,578 teach a polypeptide of SEQ ID NO:1 or a polynucleotide of SEQ ID NO:2, a variant of SEQ ID NO:1 having at least 95% identity to the sequence of SEQ ID NO:1, a variant of SEQ ID NO:2 having at least 90% identity to SEQ ID NO:2, or the complete complement of any of these sequences. Withdrawal of the rejection of claims 1-2 as being anticipated by Nagase et al. or PN=5,849,578 is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claims 1 and 3, claims 7-12 be rejoined and examined as methods of use of the polynucleotides of claims 1 and 3 that depend from and are of the same scope as claims 1 and 3 in accordance with *In re Ochiai and Brouwer* and the MPEP § 1801.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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